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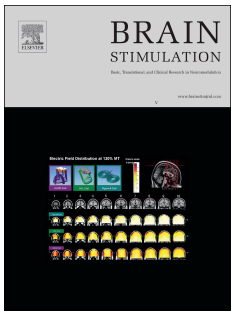

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Slow-oscillatory transcranial direct current stimulation modulates memory in temporal lobe epilepsy by altering sleep spindle generators

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Abstract

Background: Temporal lobe epilepsy (TLE) is often associated with memory deficits. Given the putative role for sleep spindles memory consolidation, the distribution of spindle generators skewed toward the affected lobe in TLE subjects may be a neurophysiological marker of defective memory. Slow-oscillatory transcranial direct current stimulation (sotDCS) during slow waves sleep (SWS) has previously been shown to enhance sleep-dependent memory consolidation possibly by increasing slow-wave sleep and modulating sleep spindles.

Objective/Hypothesis: to test if excitatory anodal sotDCS over the affected temporal lobe prior to a nap affects sleep spindles and whether this improves memory consolidation.

Methods: In this randomized controlled cross-over study 12 people with TLE underwent either sotDCS (0.75Hz; 0-250µV, 30 minutes) or a sham procedure before a daytime nap. Declarative verbal and visuospatial learning were tested. Fast and slow spindle signals were recorded by 256-channel EEG during sleep. In both study arms, we used electrical source imaging (ESI) to localize cortical generators. Neuropsychological data were analyzed with general linear model statistics or the Kruskal-Wallis test (p or $Z<0.05$), and neurophysiological data were tested with the Mann-Whitney t test and a binomial distribution test (p or $Z< 0.05$).

Results: An improvement in declarative ($p=0.05$) and visuospatial memory performance ($p=0.048$) was noted after sotDCS. SotDCS increased the current density of slow spindle generators ($Z=0.001$), with a shift to the anterior cortical areas.

Conclusions: Anodal sotDCS delivered over the affected temporal lobe can improve declarative and, to a lesser extent, visuospatial memory performance by modulating cortical source generators of slow sleep spindles. SotDCS appears to be a promising tool for memory rehabilitation in people with TLE.

Keywords: non-invasive transcranial stimulation; memory remediation; epilepsy rehabilitation; electrical source imaging; sleep spindles

Abbreviations: AEDs: anti-epileptic drugs; EEG: electroencephalography; EZ: epileptogenic zone; MRI: magnetic resonance imaging; NREM sleep: non-rapid eye movement sleep; REM: rapid eye movement sleep; MOCA: Montreal Cognitive Assessment; BDI: Beck Depression Inventory; STAY 1-2: State Trait Anxiety 1 and 2; sotDCS: slow-oscillatory transcranial direct current stimulation; tDCS: transcranial direct current stimulation; TLE: temporal lobe epilepsy.

Introduction

Temporal lobe epilepsy (TLE) is the most common form of localization related epilepsy in adults, accounting for 60% of cases [1]. It is associated with cognitive and behavioural comorbidities, and cognitive impairment is often problematic. Mesial TLE is frequently associated with memory complaints. The epileptogenic focus often originates from the hippocampus and anterior subregions (including the anterior parahippocampal cortex) [2,3,4], which are areas believed to be involved in both the encoding and consolidation of memory. Memory consolidation is thought to occur through ripples, which are fast frequency discharges (110-300 Hz) interpreted as electric discharges that promote synaptic rearrangement and replay of neural sequences learned during consolidation [5] on the basis of long-term potentiation (LTP) [6,7]. Scalp sleep spindles are believed to represent the cortical equivalent of hippocampal ripples [8,9] and to be a marker of memory consolidation [10,11,12,13]. By stimulating early gene expression and glutamate receptors, sleep spindle activity creates optimal conditions for LTP in the neocortex [14]. Spindles are generated by interactions between multiple, synchronous but independent cortical areas [15,16,17] which have been suggested to underlie the re-processing of specific memory traces in devoted brain regions [18]. In people with TLE, slow sleep spindles show a preferential generator of higher current intensity over the affected temporal lobe [19]. The exact neurophysiological and neuropsychological meaning remains speculative, but the hypothesis that this deviation from healthy volunteers' patterns constitutes a substrate for memory impairment in TLE is intriguing, since it points to either a dysfunction or a compensatory mechanism.

Transcranial direct current stimulation (tDCS) has recently gained momentum due to its easy applicability and promising early results. TDCS works by applying weak electrical currents to the scalp that induce acute modifications of neuronal membrane potentials [20,21], producing long-lasting changes in the bioelectric activity of underlying brain tissue [22] by either depolarization (anodal tDCS) or hyperpolarization (cathodal tDCS) of the resting membrane potential, usually without eliciting action potentials. Cognitive studies have shown that tDCS can enhance human waking performance, including memory, language, computational, and executive function [23,24,25,26]. Results from tDCS during sleep, with a specific time-varying stimulation, suggest that consolidation of declarative memories may occur in young healthy volunteers [23, 27] but not in an elderly population [28]. These studies used a slow oscillating tDCS (sotDCS) paradigm as the induction of oscillations by transcranial stimulation is believed to interact with ongoing oscillatory cortical activities. [29]. Animal and human studies have shown that sotDCS boosts slow oscillations during sleep and enhances memory [30,31]. Slow oscillatory activity exerts a grouping influence on faster EEG frequencies during the depolarizing up phase of these oscillations [32] and consequently entrains sleep spindles [33].

Given the strict interplay between sleep spindles and memory consolidation, with an increase in spindle density/amplitude related to better mnemonic performance [10,11,12,13,34], increasing spindles by sotDCS appears to be a promising tool. To date, most data in this area are derived from healthy volunteers, with few studies investigating these parameters in populations with neuropsychological disorders [35,36].

We hypothesized that fronto-temporal anodal sotDCS applied to the side of the discharging temporal lobe could modulate sleep spindle generators and improve mnemonic performances in people with neuropsychological disorders. We set out to test if excitatory depolarizing slow-oscillating anodal stimulation over the affected temporal lobe could affect spindles and thus improve declarative and visuospatial memory performance.

Materials and Methods

Subjects

Twelve people with pharmaco-resistant mesial TLE [38] and mesial sclerosis were enrolled in the study. As part of their pre-surgical evaluation, all had undergone standard and video-EEG, high-density (256-channel) EEG, 3T MRI with perfusion sequences and, whenever indicated, nuclear imaging studies. Excluded from the study were people with active psychiatric or neurological co-morbidity, drug treatment other than antiepileptic drugs (AEDs), and major cognitive impairment. The assessment battery included the Montreal Cognitive Assessment (MOCA) [38], the Beck Depression Inventory (BDI) [39], and the State Trait Anxiety (STAY1 and 2) [40]. The study was approved by the Ethics Committee of Verona University Hospital. All subjects provided written informed consent to participate.

Methods

A randomized controlled cross-over design was used. Subjects were randomized by a computer-generated sequence to one of the two arms. The inter-session interval was at least 1 week stable medication throughout. Group 1 received stimulation during wake before sleep during the first session and sham stimulation during the second session, and vice-versa (Fig. 1). On the recording days, all subjects were partially sleep deprived (awakened at 3 A.M.) to facilitate recording of N2 sleep and were asked to refrain from stimulants until recording was completed. All subjects arrived the study center at 11.30, where they were administered the MOCA test by the examiner during the first session of both study arms; BDI and STAY Y1 and Y2 were self-administered in between learning and recall memory testing in both sessions. After neuropsychological testing, the subjects underwent 30 minutes of either real or sham stimulation and were then allowed to sleep during 256-channel EEG recording. Lights off was set at 13.30 to control for possible circadian modulations. The subjects were allowed at least 60 minutes of sleep or 1 hour and 45 minutes of time in bed (TIB), whichever came first. Thirty minutes after awakening, verbal and visuospatial memory recall were retested to avoid sleep inertia interferences.

Neuropsychological evaluation

Declarative verbal and visuospatial memory were tested. Parallel task versions were used in the two experimental sessions. Declarative verbal memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT). The Italian adapted version of the Rey Auditory Verbal Learning Test [41] consists of a 15 noun-word list the subject has to recall immediately after each of 5 consecutive repetitions, and after a 15-minute interval (delayed recall) during which the subject has to be engaged in non-mnemonic tasks (i.e., non-verbal testing that does not interfere with recall). An additional recognition trial is performed after the recall with 45 words including the 15 words initially presented from the list plus 30 distractor items. During each session, a different noun list and distractors list was administered. In our study protocol, a free and clued (45 nouns' list) recall was requested 30 minutes after awakening to evaluate memory consolidation. Assessment included final acquisition (recalled words in trial 5 before nap, free recall [number of recalled words 15 minutes after presentation and after nap]), and retention (number of words in trial 5 before nap subtracted from the number of recalled words after the nap). For the 45-words recognition trial, assessment was based on the total number of recognized words, missed recognitions, and false recognitions (15 minutes after initial presentation and after nap).

Visuospatial memory was tested with the Rey–Osterrieth Complex Figure Test [42,43] and Rey–Osterrieth Complex Figure B [44].The procedure contemplates a copy of the given figure (Figure A or B); after 10 minutes, in which the

subject has not to be engaged in other visuo-spatial mnemonic tasks, the subject has to recall the drawing. In our protocol, figure recall was requested after 30 minutes from awakening to evaluate consolidation. Assessment included the presence, completeness and localization of elements for the Rey–Osterrieth Complex Figure Test; the number of elements, the proportion between the four principal elements, the overlaps and the precision for Rey–Osterrieth Complex Figure B. In addition, loss of information between the copy task and the memory task (short-term and long-term memory) and the forgetting rate (ratio between short-term and long-term memory performance) were calculated.

The 30 minutes lag was allowed to avoid any sleep-inertia effect that could have affected the performance. Scores are then corrected according to age and educational level of the participant - i.e., adding or subtracting additional digits obtained from a grid [41], incorporating the aforementioned data. Here, the corrections were calculated on the basis of the standard deviations from the mean value of the test scores obtained from a healthy population during the standardization procedure. This correction explains the presence of fractional scores reported in such testing.

Stimulation paradigm

Stimulation was delivered through two sponge electrodes (5x8 cm) soaked in saline solution and connected to a battery driven generator (Eldith Stimulator, Ilmenau, Germany), with the anode over the fronto-temporal scalp (approximately between F7-T3 or F8-T8) of the affected temporal lobe with the cathode positioned over the ipsilateral mastoid. A sinusoidal fluctuating current (from 0 to 250 μA, and a frequency of 0.75Hz) was applied for six 5-minute slots (total 30 minutes) with an inter-block interval of 1 minute [23]. Impedance under the stimulating electrode was kept below 2K KOhm. During the sham session, the current was ramped up and down for the first and last 20 s of the stimulation interval to mimic sensations associated with current change.

EEG recordings

Immediately after tDCS stimulation, 256-channel EEG was recorded (Electrical Geodesics, Inc., Eugene, OR) using the international 10/20 system. By virtue of the net's geodesic tension structure, all electrodes were evenly distributed on the scalp at approximately the same location in all subjects. The data were recorded against a vertex electrode reference (Cz) [45] at a sampling rate of 250 Hz and filtered off-line with a band-pass filter (0.1–70 Hz). Electrooculogram (EOG) channels were mounted on the left and right eye cantus; the sampling rate was 250 Hz, bandpass filtered at 0-100 Hz, and the sensitivity set to below 5 mV. The recordings were performed in an electrically shielded, soundproof, darkened laboratory room.

EEG source imaging

Spindle selection and averaging

This procedure has been detailed elsewhere [16,19]. In short, spindles were visually scored according to the American Academy of Sleep Medicine (AASM) guidelines [46] and marked at the exact time point of their beginning. Only those spindles were selected that did not appear to be related to other sleep figures (i.e., vertex waves, minimum distance 2 ms) or contain or be immediately preceded or followed by an epileptic discharge. EEG was segmented according to

the marker position and bandpass filtered at 10-12 Hz for slow spindles and at 12-14 Hz for fast spindles. Single electrodes containing artifacts were manually selected and interpolated using a three-dimensional spline interpolation algorithm [47] to keep the number of electrodes the same for all epochs. Segments for fast and slow spindles were averaged for each subject; a grand average over all subjects for each spindle category was calculated.

ESI localization

Low-resolution brain electromagnetic tomography (LORETA), a standardized source imaging procedure, was applied to the averaged spindles [48]. LORETA minimizes the squared norm of the Laplacian of the weighted 3D current density vector field. It incorporates the "smoothness assumption" by selecting the inverse solution of the measured data with the smoothest distribution in space [49]. The LORETA inverse solutions were implemented within the GeoSource software package (Electrical Geodesics) using the probabilistic cortical gray matter locations from the Montreal Neurological Institute (MNI) [50] probabilistic atlas (www.bic.mni.mcgill.ca). Sources were projected only on the cortical gray matter.

For each subject and for each spindle frequency, the cortical sources were calculated taking the time point at the transition from baseline to the initial deflection of the spindle, and identified in terms of Brodmann coordinates and maximum source intensity [45,51].

Statistical analysis

Neuropsychological performance was tested with a general linear model statistics for repeated measures (test pre_post stim_sham test*pre_post test*stim_sham pre_post*stim_sham test*pre_post*stim_sham), considering each sub-item of the verbal and visuospatial memory task. A correction for age, years of schooling, MOCA, epilepsy lateralization, and the order of manipulation (stimulation-sham versus sham-stimulation) was run, but given the small sample size and the significance, no more than a LSD was possible, and thus this part was excluded from further discussion. If the sample presented non-parametric data characteristics, a Kruskal-Wallis test for median comparisons was used. Differences between source intensities expressed in nA (nanoAmpére) were tested using a Mann-Whitney t test for independent samples ($Z < 0.05$), given the non-parametric characteristics of the data ($Z < 0.05$). Source generator localization between the sham and stimulation procedures was statistically compared using a binomial distribution test ($p < 0.05$).

Results

All 12 subjects (4 M; mean age 34.2±15.4 years; mean years of schooling 15.7±2.5; 2 of which with left TLE) were on sodium-channel blocking AEDS (carbamazepine, mean dose 700 mg; eliscarbazepine, mean dose 600 mg; lamotrigine, mean dose 100 mg), except for 2 subjects who were on zonisamide as add-on therapy (mean dose 150 mg).

Following the stimulation condition, total sleep time was increased (TST_stim: 54.6±11.2; TST_sham: 41.9±10.7; p=0.01) and a reduction in sleep latency (SL_stim: 13±5.8; SL_sham: 19.1±6.1; p=0.01). After the sham procedure, the mean number of fast spindles was higher than the slow spindles (p=0.03), but this difference waned in the stimulation session. No other polysomnographic parameters showed statistical significance, although a trend towards a higher sleep spindle count during sleep after stimulation was detected. The polysomnographic data are presented in Table 1.

Spindle cortical generators

The current density of the slow spindle generators was significantly increased after tDCS as compared to the sham procedure (Z=0.001), whereas no significant difference between the two conditions emerged for fast spindles (Table 3 and Table 1 Supplementary material, Fig. 2). Multiple and concomitant spindle generators for both slow and fast spindles tended to locate more anteriorly after stimulation, but the distribution did not reach statistical significance (p=0.06 and p=0.067). No effect was detectable for fast spindle generators.

Neuropsychological testing

Differences in neuropsychological test results between the condition "sleep plus tDCS" and "sleep plus sham" were evident (p=0.022) as an improvement in declarative memory after tDCS and nap, with better retention (p=0.05). Visuospatial testing demonstrated a slight reduction in forgetfulness after stimulation and nap as compared to sham (p=0.048). No other measures of declarative memory reached significance (Table 2).

Discussion

Our results suggest that anodal slow-oscillatory tDCS over the fronto-temporal area ipsilateral to the discharging lobe administered before a nap in TLE is effective in increasing declarative and, to a lesser extent, visuospatial memory consolidation. These results are supported by the finding that after stimulation the cortical slow spindle generators tended to shift to more anterior loci and displayed a higher current intensity than in the sham condition. As previously reported [23], sotDCS delivered during SWS also boosted slow wave oscillations, ameliorating polysomnographic parameters such as SL and TST.

This is in line with the observed consolidation of the hippocampus-dependent learning task, measured as the difference between performance at learning before sleep and retrieval after sleep, induced by slow wave sleep and associated slow oscillation activity dominant during early nocturnal sleep [23,52,53,54,55]. Here, we focused on sleep-related learning by taking into account N2 sleep spindles, suggested as a marker for memory consolidation during sleep [10,11,12,13]. Spindles are brief bursts of waxing and waning oscillations considered to be the hallmark of N2 sleep, described as slower frontal (10-12 Hz) and faster posterior (12-14 Hz) spindles, in both healthy and epileptic subjects [15, 56], generated independently, although synchronously, in diverse cortical areas [15,16,17].

Previously, we observed a skewed distribution of N2 slow spindle cortical generators over the affected lobe in TLE and hypothesized this to be a possible neurophysiological explanation for defective memory consolidation in TLE [19]. The observation that with pre-sleep sotDCS we could modulate the spatial distribution and intensity of these cortical sources, obtaining a concomitant amelioration of specific mnemonic tasks, supports our initial hypothesis, which could inform rehabilitative options for memory complaints in TLE.

The efficacy of sotDCS to improve declarative memory has been demonstrated mainly in healthy young volunteers [23] and recently in adults with schizophrenia [36] and children with attention deficit-hyperactivity disorder [35]. No such studies have been conducted in people with epilepsy, although an animal study on rodents reported a reduction in seizure frequency and spatial memory deficits after cathodal continuous tDCS [57]. To date, tDCS stimulation studies on people with epilepsy have applied cathodal stimulation to reduce neuronal excitability and thus reduce seizure occurrence [58,59,60,61]. Differently, our paradigm involved excitatory, oscillating stimulation that could have negatively affected the neuronal threshold over the epileptogenic zone. We did not observe seizures in any of the

subjects and none complained of increased seizure frequency in the week after stimulation. One reason for this favorable outcome could have been the low tDCS current intensity which, conversely, could explain why consolidation improvement did not reach statistical significance in all tested items.

In contrast with previously quoted studies [23], in which SOtDCS was administered during SWS in order to obtain a summative effect, we preferred a pre-sleep stimulation protocol given the rehabilitative perspective of the study.

Although SWS and concomitant SOtDCS stimulation could have produced longer-lasting and possibly more robust statistical significance, the efficacy of a tDCS protocol to be administered in an out-of-hospital setting is of paramount importance. Given the user-friendliness of tDCS, this does not appear as a remote possibility also in the realm of cognitive rehabilitation, as such would be the case. Indeed, SOtDCS application during SWS would not be an option in a domestic setting. Given our preliminary results, SOtDCS administered during wake before sleep seems promising, although further studies are needed to confirm the efficacy of home-based administration.

After sotDCS, the subjects demonstrated an increased retention of learned words (Rey Auditory Verbal Learning Test) and a lesser degree of forgetfulness in the Rey figure drawing. The modulations we report are mainly expressed as effects on N2 slow spindle amplitude. Generally, EEG signal amplitudes reflect the extent of synchrony and excitability of the underlying neural population [62]. In this view, spindle amplitude may be the epiphenomenon of local cortical activation. A recent EEG–fMRI study showed, in fact, that sleep spindle amplitude is related to reactivation of brain modules involved in prior memory consolidation [63], as well as with hippocampal activation. According to this line of research, the observed increase in the intensity of sleep spindle generators points in the same direction: sotDCS likely contributes to the reactivation process needed for memory consolidation exactly in those areas that appear to be defective in TLE. Although there was no statistically significant difference in sleep spindle count between the two conditions, the more frequent fast spindles recorded in the sham condition ($p=0.03$) subsided, with normalization to slow spindles. This indicates that oscillatory tDCS has a slight effect in increasing slow spindles and could explain the neurophysiological mechanism of memory consolidation and retention.

Finally, there was a slight shift of bilateral posterior – mainly temporo-parietal – sources towards fronto-temporal locations after sotDCS-modulation of cortical generators. We cannot explain why the posterior generators were more affected than the anterior ones. One possible reason is that slow spindles originate from frontal areas and that stimulation re-establishes a more physiological pattern with a partial reintegration of memory functions. On the other hand, current flow involved the fronto-temporal areas, strengthening these cortical sources to the detriment of the non-stimulated ones.

There are limitations to our study. All subjects were on AEDs. Treatment was unchanged throughout the study, but sodium and calcium-channel blockers are known to reduce the effects of anodal tDCS [64]. All subjects were on sodium-channel modulators including zonisamide, which also has a minor effect on calcium channels. AED treatment could thus have reduced the efficacy of stimulation, possibly accounting for the significant results seen on only a few sub-tests and with threshold significance values. The sample size was small due to the restrictive inclusion criteria we had to apply to assure data reliability. This restriction could also have influenced the results statistical significance, that was detected only for a few items with a cut-off value. Inclusion criteria implied that our subjects were well-functioning, slightly or not impaired ones (low BDI, relatively low STAY 1 and 2, MOCA into normal range). Cognitive performances could thus only slight improve, given a “ceiling effect”, and were mainly detected in the realm of the supposedly less affected hemisphere. One future direction should be to test more significantly impaired TLE

individuals to ascertain if such a stimulation paradigm allows noteworthy amelioration. Furthermore, we did not re-analyze the topographical relation of sleep spindle cortical generators with the epileptogenic zone, as this was beyond the scope of the present study.

Conclusion

Our findings suggest sotDCS to be a promising tool for use in memory rehabilitation protocols for people with TLE. This assumption rests on the hypothesis that the reinforcement of slow spindle temporal generators could be a compensatory mechanism: if memory does improve when slow spindles are more frequently generated and with a higher intensity over the temporal lobes, then this points indirectly to a causative, compensatory mechanism. Further studies in other forms of localization-related epilepsy are needed to investigate whether cognitive domains other than memory could benefit from similar stimulation paradigms.

Legend to figures

Table 1. Polysomnographic data. TST: total sleep time; SL: sleep latency; N1: non REM (NREM) sleep stage N1; N2: non REM (NREM) sleep stage N2; N3: non REM (NREM) sleep stage N1; REM: rapid eye movement sleep.

Table 2. Neuropsychological test results. MOCA: Montreal Cognitive Assessment; BDI: Beck Depression Inventory; STAY: State Trait Anxiety Inventory.

Table 3. Slow and fast spindles' source intensity for every source as calculated by ESI. Only intensities are reported, with statistical significance at the bottom of each category (slow spindles sham vs slow spindles SOtDCS; fast spindles sham vs fast spindles SOtDCS). Note the important source intensities increase for slow spindles after stimulation compared to sham (Z=0.001), whereas no major effect of SOtDCS was noticed for fast spindles. Sources MNI coordinates and anatomical localization has been reported as supplemental material.

Table 1. Supplemental material Localization, MNI coordinates and intensities of each source identified for slow and fast spindles in the two conditions.

Figure 1. Schematic representation of the study protocol and timing of interventions.

Figure 2. Grand average of source localization for slow (left column) and fast (right column) spindles in a sham and a stimulation condition. The crosshairs denote the point of maximal source. Slices were adjusted to show the maximum intensity and its area. Note the higher current intensity after SOtDCS, and a shift to more anterior cortical areas, more marked for the slow spindle generators.

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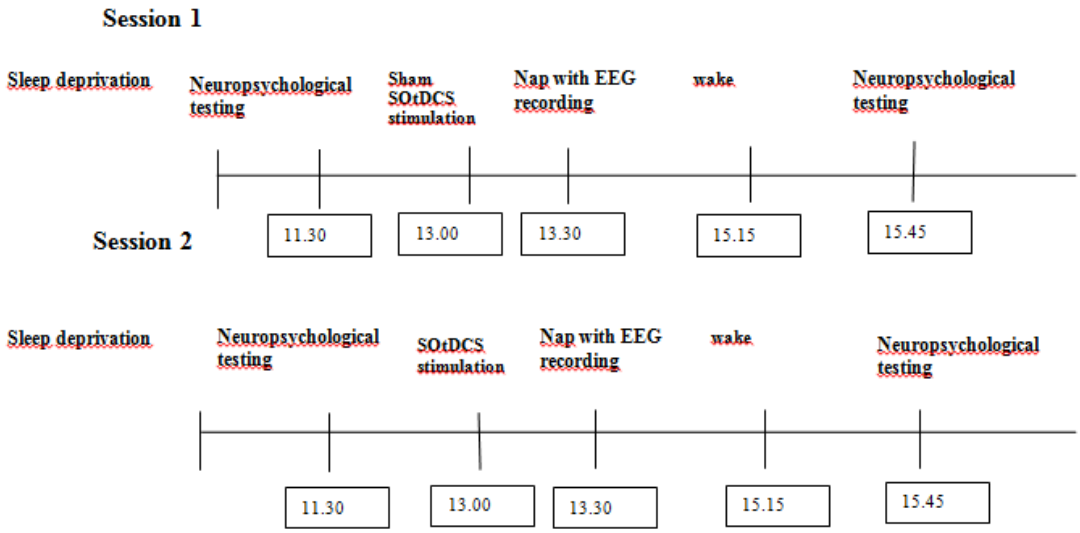
Table 1

	sotDCS	Sham	P value
TST	**54.6±5.8**	**41.9±6.1**	**0.01**
SL	**13±5.8**	**18±6.1**	**0.01**
NREM N1	9.4±3.3	9.2±2.2	NS
NREM N2	31.8±8.3	27.9±7.5	NS
NREM N3	12.3±5.1	4.9±4.2	NS
REM	0	0	NS
N° fast spindles	25±12.18	21±10.8	NS
N° slow spindles	23±5.4	19±8.8	NS

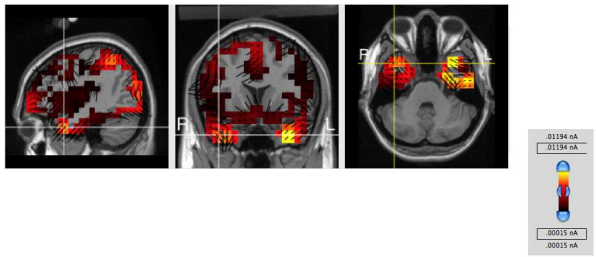
Table 2

	sotDCS	Sham	P value
MOCA	27±1		
BDI	4.4±3.9	5.8±4.2	NS
STAY1	37.7±9.5	40.4±11.1	NS
STAY 2	37±15	37.8±15.9	NS
Retention	**-0.4±1.4**	**-1.5±1.1**	**0.05**
Recollection	9.8±2	8.8±2.9	NS
Recognition	13.8±0.8	13±1.9	NS
Missed recognitions	1.1±0.9	2±1.9	NS
False recognitions	1±1	1.1±0.9	NS
Rey figure recollection after 10'	20.7±3.3	19.6±5.8	NS
Rey figure recollection after nap	18.2±3.8	19.6±5.8	NS
Loss of information	15.4±9.9	17.1±14.3	NS
Forgetting rate	**- 7.6±9.6**	**6.5±3.6**	**0.048**

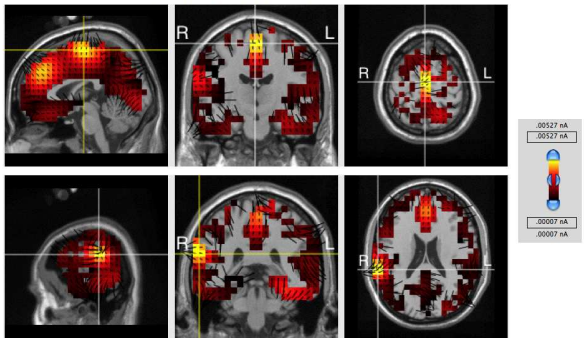
	Slow spindles sham	Slow spindles SOtDCS	Fast spindles sham	Fast spindles SOtDCS
Subject 1	**Intensity (nA)**	**Intensity (nA)**	**Intensity (nA)**	**Intensity (nA)**
	0.0066	0.0167	0.0213	0.0111
	0.0089	0.0114	0.0256	0.0090
	0.0080	0.0120	0.0228	0.0080
	0.0030			
Subject 2	0.0094	0.0329	0.0191	0.0089
	0.0157	0.0300	0.0146	0.0076
		0.0217	0.0153	0.0036
Subject 3	0.0075	0.0006	0.0075	0.0041
	0.0063	0.0042	0.0062	0.0047
	0.0063	0.0044	0.0055	0.0053
	0.0054	0.0043		0.0051
				0.0035
	0.0114		0.0095	0.0119
Subject 4	0.0100	0.0195	0.0097	0.0114
	0.0083	0.0105	0.0072	0.0126
		0.0167	0.0047	
		0.0098		
	0.0092		0.0206	0.0013
Subject 5	0.0071	0.0917	0.0133	0.0111
	0.0077	0.0647	0.0224	
	0.0087	0.0810		
Subject 6	0.0184	0.0206	0.0162	0.0082
	0.0164	0.0133	0.0143	0.0085
	0.0115	0.0224	0.0129	0.0079
Subject 7	0,0126	0.0230	0.0074	0.0093
	0.0116	0.0134	0.0068	0.0090
	0,0036	0.0158	0.0086	0.0079
	0,0087	0.0209	0.0068	0.0077
			0.0078	
			0.0077	
Subject 8	0,0071	0,0178	0.0076	0,0056
	0,0045	0,0098	0.0056	0,0073
	0,0015	0,0287	0.0176	0,0967
				0,0067
Subject 9	0,0076	0,0079	0.0167	0,0098
	0,0063	0,0098	0.0045	0,0167
	0,0143	0,0167	0.0069	0,0067
	0,0056	0,0276	0.0092	0,0123
	0,0111			
Subject 10	0,0075	0,0368	0.0276	0,0034
	0,0036	0,0324	0.0156	0,0115
	0,0056	0.0099	0.0067	0,0098
		0,0153	0.0193	0,0111
		0,0189		
		0,0256		
Subject 11	0,0045	0,0254	0.0056	0,0056
	0,0112	0,0156	0.0149	0,0231
	0,0045	0,0078	0.0063	0,0239
	0,073	0,0476		
		0,0087		
Subject 12	0,0089	0.0256	0.0084	0,0043
	0,0045	0.0189	0.0082	0,0076
	0,0078	0.0222	0.0048	0,0065
	0,0035	0.0178	0.0176	
	0,0087			
	0,0023			
		Z=0.001		**NS**



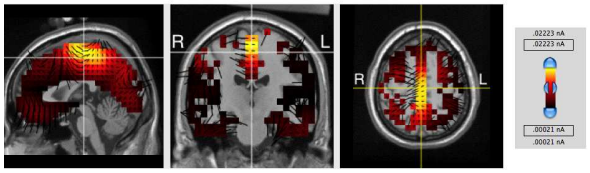
Slow spindles sham



Slow spindles sotDCS



Fast spindles sham



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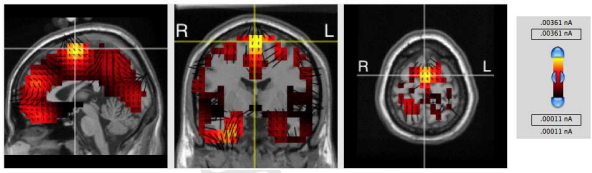

Highlights

- Slow oscillatory transcranial direct current stimulation (sotDCS) improves memory consolidation across a nap in people with temporal lobe epilepsy
- SotDCS affects slow sleep spindle cortical generators, increasing current density and shifting them to more anterior cortical areas
- Unilateral fronto-temporal sotDCS is likely to influence bilateral temporal lobes both through inter-hemispheric connection and epileptogenic networks pathways

	Spindle 10-12 Hz SHAM				Spindle 10-12 Hz SOtDCS				Spindle 12-14 Hz SHAM				Spindle 12-14 Hz SOtDCS			
Subject 1	**lobe**	**gyrii, Brodmann area**	**Talairach coordinates**	**Intensity (nA)**	**lobe**	**gyrii, Brodmann area**	**Talairach coordinates**	**Intensity (nA)**	**Subject**	**lobe**	**gyrii, Brodmann area**	**Talairach coordinates**	**Intensity (nA)**	**lobe**	**gyrii, Brodmann area**	**Talairach coordinates**	**Intensity (nA)**
	L frontal	medial frontal (6)	-3,-4,-64	0.0066	L parietal	superior parietal lobule (7)	-17,-60,64	0.0167	**Subject 1**	L parietal	precunesu (7)	-3,-46,50	0.0213	L parietal	precuneus (7)	-10,-53,64	0.0111
	R frontal	subgyral (6)	25,-4,57	0.0089	R temporal	inferior temporal (20)	46,-4,-46	0.0114		L frontal	medial frontal (6)	-3,-11,64	0.0256	L parietal	inferior parietal lobule (40)	-38,-53,5	0.0090
	R parietal	parietal lobule (40)	32,-53,57	0.0080	L temporal	inferior temporal (20)	-52,-4,-34	0.0120		L frontal	paracentral lobule (5)	-3,-46,64	0.0228	L frontal	medial frontal (6)	-3,-11,64	0.0080
				0.0030	R frontal	orbital (11)	4,45,-20										
Subject 2	L frontal	superior frontal (6)	25,3,37	0.0094	L limbic	uncus (20)	-38,-11,-34	0.0329		R temporal	inferior temporal (20)	53,-11,-34	0.0191	L frontal	medial frontal (6)	-3,-11,64	0.0089
	L temporal	middle temporal (21)	-45,10,-34	0.0157	L frontal	medial frontal (6)	-3,-11,64	0.0300	**Subject 2**	L limbic	uncus (20)	-31,-11,-34	0.0146	L frontal	paracentral lobule (5)	-3,-39,57	0.0076
	L frontal	medial frontal	-3,17,50					0.0217		L frontal	medial frontal (6)	-3,-11,64	0.0153	L frontal	medial frontal (11)	-3,59,-13	0.0036
Subject 3	L temporal	inferior temporal (20)	-52,-4,-34	0.0075	R frontal	middle frontal (6)	32,-4,57	0.0006		R frontal	medial frontal (11)	4,38,-20	0.0075	R temporal	inferior temporal (20)	39,-11,-41	0.0041
	L frontal	medial frontal (6)	-3,-4,64	0.0063	L limbic	uncus (amigdala)	-24,-4,-27	0.0042	**Subject 3**	R temporal	middle temporal (21)	53,3,-20	0.0062	L limbic	uncus (20)	-31,-11,-27	0.0047
	L frontal	medial frontal (11)	-3,38,-20	0.0063	L temporal	inferior temporal (20)	-52,-4,-34	0.0044		L frontal	medial frontal (8)	-3,24,50	0.0055	R frontal	medial frontal (11)	4,38,-20	0.0053
	L occipital	cuneus (18)	-3,-74,15	0.0054	L temporal	fusiform (37)	-52,-46,-27	0.0043						L temporal	middle temporal (21)	-66,-25,-13	0.0051
														R frontal	medial frontal (6)	4,-18,64	0.0035
				0.0114	L frontal	medial frontal (6)	-3,-4,64		**Subject 4**	L frontal	superior frontal (8)	-3,31,50	0.0095	L frontal	medial frontal (10)	-3,59,-6	0.0119
Subject 4	L frontal	medial frontal (11)	-3,38,-20	0.0100	L frontal	medial frontal (9)	-3,45,29	0.0195		L temporal	superiortemporal (38)	-38,10,-34	0.0097	L limbic	anterior cingualte (32)	-3,38,29	0.0114
	L frontal	medial frontal (8)	-3,38,43	0.0083	L frontal	medial frontal (11)	-3,38,-20	0.0105		R frontal	superior frontal (10)	18,66,-6	0.0072	L frontal	medial frontal (6)	-3,3,64	0.0126
	L temporal	superior temporal (38)	-38,10,-34					0.0167		L frontal	paracentral lobule (4)	-3,-39,64	0.0047				
	R temporal	superior temporal (38)	39,10,-34					0.0098									
				0.0092	L frontal	medial frontal (6)	-3,-11,64		**Subject 5**	L temporal	inferior temporal (20)	67,-39,22	0.0206	L temporal	fusiform (20)	-52,-39,-27	0.0013
Subject 5	L frontal	medial frontal (11)	-3,38,-20	0.0071	L occipital	precuneus (31)	-3,-74,29	0.0917		R temporal	inferior temporal (20)	-3,11,64	0.0133	R frontal	medial frontal (10)	-3,59,-6	0.0111
	L parietal	superiori parietal lobule (7)	-17,-535,64	0.0077	L parietal	inferior parietal lobule (40)	67,-32,22	0.0647		R frontal	superior frontal (8)	-52,-39,-20	0.0224				
	L temporal	fusiform (20)	-59,-11,-27	0.0087	L temporal	inferior temporal (20)	46,-4,-41	0.0810									
Subject 6	R temporal	superior temporal (22)	67,-39,22	0.0184	L frontal	orbital (11)	-3,45,-20	0.0206	**Subject 6**	R parietal	inferior parietal lobule (40)	67,-32,29	0.0162	R parietal	precuneus (7)	4,-53,50	0.0082
	L frontal	medial frontal (6)	-3,11,64	0.0164	L frontal	middle frontal (10)	-38,52,8	0.0133		R frontal	inferior frontal (45)	53,31,8	0.0143	L parietal	inferior parietal lobule (40)	-38,-53,50	0.0085
	L temporal	inferior temporal (37)	-52,-39,-20	0.0115	L frontal	superior frontal (6)	-3,10,57	0.0224		L parietal	precuneus (7)	-3,-53,57	0.0129	L frontal	middle frontal (8)	-31,24,50	0.0079
Subject 7	L limbic	uncus (20)	-31,-11,-27	0,0126	L frontal	medial frontal (25)	-3,31,-20	0.0230	**Subject 7**	L occipital	lingual (18)	-3,-88,-6	0.0074	R frontal	superior frontal (8)	4,24,57	0.0093
	L parietal	preuneus (7)	-2,-81,43	0.0116	L temporal	inferior temporal (37)	-52,-39,-20	0.0134		L temporal	superior temporal (38)	-38,10,-34	0.0068	R frontal	paracentral lobule (5)	4,-46,57	0.0090
	L frontal	medial frontal (8)	-3,24,50	0.0036				0.0158		R limbic	uncus (20)	49,-11,-34	0.0086	R parietal	inferior parietal lobule (40)	32,-53,57	0.0079
	R frontal	inferior frontal (10)	39,52,1	0,0087				0.0209		L frontal	medial frontal (11)	-3,38,-20	0.0068	L temporal	inferior temporal (37)	-52,-39,-20	0.0077
										L frontal	superior frontal ((6))	-3,10,57	0.0078				
										L parietal	precuneus (7)	-3,-53,57	0.0077				
Subject 8	R temporal	superior temporal (38)	39,10,-34	0,0071	R frontal	inferior frontal (10)	39,52,1	0,0178	**Subject 8**	R frontal	inferior frontal (45)	53,31,8	0.0076	R temporal	middle temporal (21)	53,3,-20	0,0056
	R limbic	anterior cingualte (32)	-3,38,29	0,0045	R temporal	middle temporal (21)	53,3,-20	0,0098		R temporal	superior temporal (38)	39,10,-34	0.0056	R parietal	parietal lobule (40)	32,-53,57	0,0073
	L parietal	inferior parietal lobule (40)	67,-32,22	0,0015	L frontal	medial frontal (8)	-3,24,50	0,0287		L temporal	inferior temporal (37)	-52,-39,-20	0.0176	R limbic	uncus (20)	-31,-11,-27	0,0967
	L occipital	precuneus (31)	-3,-74,29		R frontal												
														L temporal	inferior temporal (37)	-52,-39,-20	0,0067
Subject 9	L frontal	medial frontal (8)	-3,24,50	0,0076	L frontal	medial frontal (11)	-3,38,-20	0,0079		L frontal	medial frontal (6)	-3,-11,64	0.0167	L temporal	fusiform (20)	-52,-39,-27	0,0098
	L frontal	medial frontal (6)	-3,-11,64	0,0063	L frontal	superior frontal ((6))	-3,10,57	0,0098	**Subject 9**	L parietal	preuneus (7)	-2,-81,43	0.0045	L frontal	medial frontal (6)	-3,11,64	0,0167
	L temporal	superior temporal (38)	-38,10,-34	0,0143	L temporal	inferior temporal (37)	-52,-39,-20	0,0167		R frontal	subgyral (6)	25,-4,57	0.0069	R parietal	precuneus (7)	4,-53,50	0,0067
	L limbic	uncus (20)	-31,-11,-27	0,0056	R temporal	superior temporal (38)	39,10,-34	0,0276		R parietal	inferior parietal lobule (40)	32,-53,57	0.0092				0,0123
	L parietal	precuneus (7)	-10,-53,64	0,0111													
Subject 10	R temporal	inferior temporal (20)	46,-4,-46	0,0075	R frontal	inferior frontal (10)	39,52,1	0,0368	**Subject 10**	R parietal	inferior parietal lobule (40)	32,-53,57	0.0276	R parietal	precuneus (7)	4,-53,50	0,0034
	R parietal	inferior parietal lobule (40)	32,-53,57	0,0036	R frontal	medial frontal (11)	4,38,-20	0,0324		R limbic	uncus (20)	17,-3,29	0.0156	L parietal	preuneus (7)	-2,-81,43	0,0115
	L occipital	cuneus (18)	-3,-74,15	0,0056	R temporal	superior temporal (22)	67,-39,22	0,0099		R temporal	superior temporal (38)	39,10,-34	0.0067	L temporal	superior temporal (38)	-38,10,-34	0,0098
					R temporal	middle temporal (21)	53,3,-20	0,0153		L limbic	uncus (20)	-31,-11,-27	0.0193	L frontal	superior frontal ((6))	-3,10,57	0,0111
					L temporal	superior temporal (38)	-38,10,-34	0,0189									
					L limbic	uncus (20)	-31,-11,-27	0,0256									
Subject 11	R temporal	inferior temporal (20)	46,-4,-46	0,0045	R temporal	superior frontal ((6))	-3,10,57	0,0254	**Subject 11**	L frontal	medial frontal (11)	-3,38,-20	0.0056	L limbic	uncus (amigdala)	-3,21,-12	0,0056
	L frontal	medial frontal (11)	-3,38,-20	0,0112	R frontal	inferior frontal (10)	39,52,1	0,0156		L frontal	superior frontal (8)	-3,31,50	0.0149	R limbic	uncus (20)	-31,-11,-27	0,0231
	R temporal	inferior temporal (20)	46,-4,-46	0,0045	R frontal	medial frontal (11)	4,25,40	0,0078		L limbic	uncus (20)	-31,-11,-27	0.0063	L temporal	superior temporal (38)	-38,10,-34	0,0239
	L limbic	uncus (20)	-31,-11,-27	0,073	L limbic	uncus (20)	-31,-11,-27	0,0476									
					L temporal	superior temporal (38)	-38,10,-34	0,0087									
Subject 12	L limbic	uncus (20)	-31,-11,-27	0,0089	R frontal	inferior frontal (10)	39,52,1	0.0256	**Subject 12**	R parietal	inferior parietal lobule (40)	32,-53,57	0.0084	L parietal	superiori parietal lobule (7)	-17,-535,64	0,0043
	L parietal	preuneus (7)	-2,-81,43	0,0045	L frontal	superior frontal ((6))	-3,10,57	0.0189		L frontal	medial frontal (8)	-3,24,50	0.0082	L frontal	medial frontal (6)	-3,-11,64	0,0076
	R occipital	lingual (18)	4,-88,-6	0,0078	L temporal	fusiform (20)	-59,-11,-27	0.0222		R limbic	uncus (20)	-31,-11,-27	0.0048	L limbic	uncus (20)	-31,-11,-27	0,0065
	R parietal	inferior parietal lobule (40)	32,-53,57	0,0035	L frontal	medial frontal (8)	-3,24,50	0.0178		L limbic	uncus (amigdala)	-3,21,-12	0.0176				